Key Issues Dialogue: Immunoglobulin
Featuring thought leaders in the primary immune deficiency and neurological disease communities

Biotherapies for Life™ CSL Behring
London participants (L to R): Chris Hughan, Dr. Michael Rode, David Watters, Martine Pergent, Johan Prevot, Dr. Hans-Peter Hartung, and Gerd Klock
Key Issues Dialogue: Immunoglobulin

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Leaders in two different therapeutic communities—primary immune deficiencies (PID) and neurological diseases including Guillain-Barré Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)—recently gathered via high-resolution virtual telepresence in London and New York to explore commonalities and differences in their professional experiences, to discuss the key issues facing patients in these communities and to propose solutions for continuing to improve the future for people with those rare conditions.

Education and Diagnosis

DENNIS JACKMAN: It is difficult to diagnose rare disease conditions. What can be done about this?

DAVID WATTERS: The starting point has to be educating primary care doctors.

DR. RICHARD LEWIS: A primary care doctor becomes a triage officer. With neurological disorders, we have disorders that are difficult to define and difficult to diagnose—sometimes even for specialists.

CHRIS HUGHAN: Where I live, a group of doctors sees one PID patient in 10 years. We’re looking at systems that alert doctors to the possibility of a PID case. We’re looking for an alert system that will sit on their patient database and will red-flag PID patients when they conduct a regular patient audit.

DR. MEL BERGER: Sometimes sub-specialists in adult medicine, particularly pulmonology and otolaryngology, diagnose patients with Chronic Obstructive Pulmonary Disease (COPD) when these patients actually have PID. Getting those specialists to recognize the underlying diagnosis is one of our challenges and opportunities.
MARCIA BOYLE: Our foundation has a fun but very meaningful campaign called “Think Zebra.” In medical school, physicians are taught that when you hear hoof beats, think horses; think of the most usual cause of the most usual diagnosis. Immunologists are taught when they hear hoof beats to think zebras. Look for the unusual. It’s a way to increase awareness of PID.

VICKI MODELL: I think that if you don’t look, you won’t see. If we ask our primary care physicians to think that way, it’s very effective.

DAVID: In a number of countries around the world, there are no treatment facilities for adults. The focus is on children, but when those children grow up, they have nowhere to go. That’s certainly the case across Europe and other countries.

MARCIA: In the US there are more pediatricians treating patients and there are some areas where adult patients don’t have access to a specialist.

DR. JOHN SLEASMAN: It’s a two-fold problem: one is the aging child. They tend to stay with their pediatricians for years, but later develop adult complications and don’t have specialists to treat them. The second important issue is the unrecognized adult onset, particularly with common variable immune deficiencies that are primarily seen as pediatric diseases and are often missed in adults. There’s often a decade or more in which they have symptoms, but a diagnosis of immune deficiency was never made. It’s a major problem.

PATRICIA BRYANT: The same thing is happening with diagnosis of GBS and also with CIDP and related disorders. For CIDP, people usually go to their primary physicians first because of slower onset. With GBS, there is acute onset and symptoms are still not being recognized. We’re also having problems with diagnosis and referral to neuromuscular specialists. We have initiated, thanks to a medical advisory board, a program through which we designate facilities and medical practices as centers of excellence where our patients know they can receive diagnosis and treatment from specialists.

MARTINE PERGENT: In France we have a national Reference Center and a network of regional competence centers where specialized physicians work together on the national and regional levels, and where the needs of PID patients, both children and adults, can be addressed. In emerging countries it’s important to get pediatricians educated about PID. They also need analysis facilities to verify diagnoses.

DR. HANS-PETER HARTUNG: In Germany, we are facing a very serious shortage of doctors entering neurology. It’s estimated that 50% of all positions are not filled. With 82 million people there are only a few university centers with an interest in immune neuropathy. We are educating our colleagues in general neurology throughout the country. This includes training and offering courses to pediatricians about PID.
and other diseases. We liaise with our European colleagues in similar situations. At professional meetings emphasis is on courses addressing neuropathies, immune neuropathies and myopathies. It’s extremely important to establish reference centers such as GBS/CIDP Foundation International’s Core Centers of Excellence. Primary physicians and primary neurologists act as gatekeepers who watch for the red flags and find ways to channel people into the appropriate treatment.

JOHAN PREVOT: Countries with efficient reference centers generally have higher diagnosis rates because the reference centers have a dialogue with general practitioners. In Germany, there is currently an ongoing physician-led program that seeks to improve the link between general practitioners and reference centers to improve diagnosis rates. This is so critical; the consequences of late diagnosis on health care systems are tremendous.

I’m sure that primary care physicians and pediatricians would be happy to refer their patients if they knew there was a reference center in the region. Some general practitioners (GPs) just do not know about the existence of reference centers.

MARTINE: In France, not every GP knows about the reference centers. It depends on the region. Also, doctors are generally not pleased to lose patients.

DAVID: Isn’t the problem really that doctors can get lots of funding for research, but they can’t get money for making their existence known to primary care physicians? At the European Society for Immunodeficiencies (ESID) conference in Istanbul, we heard about wonderful research but we didn’t hear a great deal from the immunologists about how they spread the word in their local communities and in their countries. Immunologists have a big part to play. I know of a small immunology clinic where immediately after the immunologist arrived, he communicated with specialists in the area. That had a dramatic effect. I’m quite sure that in the parts of the country where the diagnostic rates are higher, it’s because the specialist made his practice known.

VICKI: We also need to support and encourage young physicians who show interest in immunology and specifically, primary immunodeficiency diseases. One of our greatest challenges is educating and encouraging them to stay in this field.

JOHN: In medical school education, there is a shift away from sub-specialties toward primary care which is good, but it dilutes the training. We’re not really training them in basic immunology and basic neurology. Neurology and immunology have a mystique that’s difficult to grasp for first year medical students. We need to engage the first and second year students and get them into the laboratories and clinics.

MEL: We have a number of successful programs in the US, including the PID summer school run by the US Immunodeficiency Network (USIDNET). CSL Behring has established a young faculty support grant, which supports a young investigator for three years. We
need to include something in the medical school curriculum to raise medical students’ awareness of basic immunology, clinical neurology, immunopathology and mechanisms of inflammation.

**CHRIS:** In the UK, we’ve set up bursaries for medical students wishing to conduct a research study on PID for a year as part of their intercalated degree course. We’re trying to find the best students and give them hands-on experience with PID so that they take a longer term interest and consider immunology as a career path.

**RICHARD:** Another obstacle is that medical students often finish with loans and so they look for an area of specialty that will meet their financial needs. The neurology world is not usually among the higher paying specialties. We have about a dozen students a year who want to go into neurology, but where is the research money? In neuroimmunology research, money favors multiple sclerosis over immune neuropathies. If you’re a researcher you have to go where the money is.

**FRED MODELL:** I think that you have to address these issues with a wide band of programs and certainly include physician education. You have to offer symposia and encourage the primary care physicians and the sub-specialists to have their antennae up and think about primary immunodeficiency disease. We have to have patient support and programs that engage patients so that they can talk to one another and help one another. There have to be programs of awareness; in the US, we do public service advertising. We also need research programs that address complicated diagnoses and advocacy initiatives to ensure that government officials know that rare diseases affect a large number of people.

**Reimbursement**

**DENNIS:** Have you seen reimbursement issues directly affect proper patient care?

**PATRICIA:** Every single day.

**MARCI A:** Absolutely. All the time.

**VICKI:** Yes. Every day.

**RICHARD:** We cannot see a patient and then have the remaining care provided by a doctor closer to the patient’s home and still be covered by insurance. At our center of excellence developed by the GBS Foundation, I receive calls from people out of my network so I can’t help them. There aren’t any experts within their own network, but insurance plans in the United States don’t allow them to go out of network without fighting so hard that it becomes a real obstacle. We have difficulty getting people with specific rare diseases to the right specialists.

**JOHN:** The science in clinical care always runs ahead of the insurance companies. Not long ago, it was almost impossible to give immunoglobulin (Ig) in outpatient settings...
because some insurance companies wouldn’t reimburse it. The insurance companies would only reimburse it in an inpatient setting where the costs were sometimes five to ten times higher. Then we had to run the gauntlet with subcutaneous Ig between the pharmacies and the health care systems. Eventually they catch up and see the whole picture and then realize that a subcutaneous therapy is actually saving a patient’s time and reimburse the cost of self-infusion.

**MARCIA:** Medicare will not pay for intravenous Ig (IVIg) in the home. Thankfully, there’s now subcutaneous. But for those instances when the patient or the physician thinks it’s better to be on IVIg, they don’t have a choice. It’s Medicare and the insurance companies that determine the site of care. We have an example of a man with Common Variable Immunodeficiency (CVID) in his 70’s. He was diagnosed late, a classic story of physicians missing the diagnosis and not wanting to believe it even though he has three grandsons with CVID. He has to travel a couple of hours by ambulance to Boston for infusion. Medicare will pay for that, but they will not pay for the IVIg in his home. That’s how strange the rules can be.

**PATRICIA:** They’re getting stranger and not only with Medicare. It even differs by state. Suddenly, benefits are being cut and payments denied. Because of these cuts, patients are experiencing longer intervals between IVIg treatments. The patients never get back to that point where they left off when they were getting infusions on a regular basis. It’s a nightmare, and I don’t see it getting better anytime soon.

**MEL:** Access to subcutaneous treatment at home, in comparison to intravenous treatment in a clinic, infusion center or a hospital can have very important effects on the microeconomics of a patient’s family. This includes the patient’s quality of life, the impact of the patient’s illness on the rest of the family and on the healthcare system. These issues need to be considered for neuromuscular diseases where it’s more difficult for some patients to move around or travel to a hospital or clinic. Treatments administered at home have a number of benefits across a family and within the healthcare system.

**MARCIA:** I want to touch on the issue of primary care physicians who manage and coordinate care for PID patients and who may have a disincentive for referring them to a specialist because it’s all about reimbursement. When Medicare reimbursement changed, we conducted in-depth surveys to quantify that patient locations were being shifted and the patients were having adverse outcomes. The intervals between treatments were being increased, the amounts were being decreased and patients were going off Ig. We had to quantify these data as part of our advocacy.

**PATRICIA:** We are finding that patients in some states are being taken from home infusion and pushed into a hospital. For somebody with a compromised immune system, a hospital is not the best place to be. We’re also seeing problems with
reimbursement of home care. Medicare will take care of IVlg, but won’t provide the reimbursement for ancillary materials and for nurses, etc. You have a problem in situations when patients don’t have insurance or they lose insurance. Then what happens? Do they make mortgage payments or have their IVlg infusion?

**Richard:** I have some patients who have a co-pay. For a drug that’s $100 a month they can usually afford $10-$15, but a co-pay for an Ig breaks the bank. I have some patients whose insurance keeps changing. One insurance company pays for it; the next one makes them jump through hoops, in which case they’re not getting the infusion. They go downhill, and they then end up with health changes that require them to need treatment they didn’t need before. I’ve seen that happen.

**Hans-Peter:** In Germany, we have a dual system, strictly hospital-based and private practicing physicians with a budget. They don’t want to have expensive patients because that causes trouble in seeking reimbursement. We receive calls from CIDP patients across Germany asking are you ready, willing and capable of delivering IVlg to us? They travel great distances when they can’t get it near their homes. When there is an obvious indication for CIDP, the insurance companies are very reluctant to pay for IVlg in paraproteinemic neuropathies, for example. You can get around this, but it takes months of paperwork and patients get worse. We need a joint commitment and action by industry, patient groups and physicians.

**Dr. Michael Rode:** In Germany, physicians in practice are sometimes reluctant to treat a PID patient due to the high costs of treatment. First, the patient needs to be properly diagnosed to get reimbursement for the Ig medication. But in a second step, the Association of Statutory Health Insurance Physicians compares the spending on medication of the treating physician with that of his or her peers. In cases of large deviations from the average of the peer group, the physician may have to pay the difference out of his or her own pocket. There are concerns about the possibility that so-called expensive patients get no access to treatment. A solution would be to exclude them from budget calculations. The whole community will have to work on this.

**Gerd Klock:** In Germany, we still have a number of problems in how we treat adult patients. There are still a lot of things to work out, especially for the physicians—a lot of paperwork and also the risks to their own budgets if they treat these patients. The system needs improvement, especially with rare disease patients.

**Michael:** The German PID patient association DSAI is doing some lobbying. We try to inform people involved in the system. One major step here is the FindID program where we try to invite all the stakeholders from the outpatient segment in an area and teach them diagnosis and treatment of the disease and, with help from an insurance representative, the proper documentation of the whole process. Documentation is a key element in the process!
**DAVID:** This isn’t only affecting PID patients. It’s all patients with rare disorders who are on high-cost products and there is great value in working together and talking with a much louder voice.

**MARCIA:** In the US, with Medicare reimbursement, we’re working with GBS/CIDP and others. The Jeffrey Modell Foundation (JMF) has been very helpful. If you bring all the groups together, you can be heard. There’s strength in numbers and every group has its own strengths.

**Centers of Excellence/Treatment Points of Service**

**DENNIS:** *What are some point of service options for patients, and how do centers of excellence and reference centers relate to treatment options?*

**JOHN:** For PID diseases, there’s a model we could build based on centers of excellence. We need a system in which patients could be treated locally with guidance from a center of excellence. This will ultimately keep costs down and better utilize plasma products along a clinical pathway.

**MEL:** An advantage of centers of excellence is identification of best practices and optimal care. If centers are willing and are prompted by foundations and government supporters to compare outcomes and examine programs that work, then other centers can rapidly implement those programs.

**FRED:** The Jeffrey Modell Foundation designates academic medical centers and teaching hospitals with expert physicians who treat a large number of patients with primary immunodeficiency. The process begins by designating the center as part of the Jeffrey Modell Physician Referral Network, and then some of the centers will become a named Jeffrey Modell Diagnostic and Research Center. At the same time, we create regional awareness programs that drive referrals to these specialists. We then request the immunologist to complete a survey and examine patient history prior to diagnosis, including the number of illnesses and school/work days missed, and to quantify them. The results show dramatic economic consequences. There is no question that it’s in everyone’s best interest, both on the human side and on the economic side, to properly diagnose, appropriately intervene and adequately treat these patients.

**Access**

**DENNIS:** Do you feel as physicians that you and patients have the flexibility to choose sites of service for care? For instance, if you think a home care provision is better than a hospital setting, is that truly an option? Does reimbursement allow for that on both sides of the Atlantic?

**JOHAN:** On the site of service issue in Europe, we see great differences between countries. A great initiative in France was the publication of an official government guideline paper that recommends hospitals deliver the therapy of choice according to
the wishes of the physician and the patient. It’s very difficult to implement, but it’s an example worth noting of how a government is trying to provide the right therapy for the patient.

**MARTINE:** In France, we advocated with the public health authorities to have subcutaneous therapy and IVIg at home. Afterwards, we had to deal with the doctors who were not used to their patients being treated with plasma products in their homes. It was also a challenge to organize training for patients in home infusion. In addition, we recognized that hospital pharmacies are important stakeholders; we have to deal with them and they have to deal with tender markets. It’s a big issue for us because we don’t know what kind of Ig we will have next year, or even next month.

**CHRIS:** In the UK, we had a government investigation into the use of IVIg and we petitioned very early as a patient organization with a group of doctors to ensure that PID patients receive the treatment they need. As a result of our advocacy in the UK, PID patients have been red-boxed for the Ig treatment they should receive, regardless of the amount of IVIg available. During potential shortages, this is a great reassurance for PID patients. This took a lot of work. We now have regularly updated guidelines issued by the government on treatments with IVIg and PID patients are the highest priority. We’ve just had a similar outcome in Scotland.

**GERD:** A couple of years ago we also did a lot of political campaign work and tried to convince people that it’s important to accept subcutaneous applications in Germany. Today, it’s mostly a decision between the patient and the doctor.

**RICHARD:** At an inflammatory neuropathy meeting in Australia, the Dutch group presented a paper showing that home infusion of IVIg is as safe and as effective as hospital-based therapy. Europe is coming around. Hopefully they can move things around so it happens more often. In the US, we have known this for many years. The only impediment is the insurance companies that prevent it. This is quite upsetting.

We’re trying to learn about subcutaneous in the neurological world, but there aren’t a lot of studies yet. Most likely, we’re going to find that a group of patients will still find the intravenous approach optimal because they need a higher dose. The questions will always be whether subcutaneous works for them and how much time they need for subcutaneous infusion. The benefits may not be the same as in the PID population.

**MEL:** CSL Behring is doing research in subcutaneous with some of the neurological indications. We have several investigator-initiated studies in different countries and plan to start a study on CIDP. We have also learned that a benefit of subcutaneous treatment in primary immune deficiency in some neurological diseases is that patients who receive treatment in hospitals or centers have a so-called wearing off effect. When the US Immune Deficiency Foundation took a survey, approximately two-thirds
of the patients said they can sometimes or always feel their IVlg wearing off before the next dose is due. We believe there are patients with the neuro and immune inflammatory diseases who are also feeling themselves becoming weaker and less able to do some of their activities. The ability to get an infusion at home without being dependent on transportation or on the availability of the hospital would make a big difference in their lives.

**DENNIS:** *Do treatment guidelines help? Where and what needs to be done to make sure that those guidelines are appropriate?*

**HANS-PETER:** Guidelines are helpful, particularly when one looks at the accessibility of patients to modern and more costly therapies. With regard to IVlg treatment of CIDP, the guidelines endorsed by the German Society of Neurology and by the European Federation of Neurological Societies (EFNS) have been instrumental in providing the momentum and the arguments for physicians to use drugs that have shown efficacy. It’s extremely important for patients to have early access and this is supported by guidelines. Physicians can also use them to defend their decision against insurance companies.

**CHRI$$:** In general, the UK guidelines have been very beneficial and they certainly seem to be working at the moment. We’re monitoring them closely to confirm if that is the case. Certainly, in terms of patient and physician concerns, guidelines are working well. The acid test will be what happens if there are shortages.

**JOHAN:** The International Patient Organization for Primary Immunodeficiencies (IPOPI) has been particularly verbal about making sure that in times of shortages there would be a hierarchy of indications applied so that products go to patients with priority indications. Immunoglobulins are like wonder drugs and you have an almost endless array of indications and new indications popping up every day. We also know that with biological products, shortages are a recurrent issue. As a patient group, we want to make sure that, particularly in shortages, there is a hierarchy of indication. Most government guidelines put PID and GBS high on the list.

**DENNIS:** *What else can we do to help assure Ig supply to patients?*

**BERNADINE DIXON:** At CSL Behring, we have invested in production optimization, additional capacity and development of new state-of-the-art immunoglobulin products. Technological advances help us further ensure product supply and safety. CSL Behring’s substantial investment in our Bern, Switzerland facility, our Center of Excellence for immunoglobulins, was recognized by the Swiss government with a Tell Award for Switzerland’s most significant innovative technology investment in 2008. Our plans and investments are there to improve the patient experience.
MEL: I think that another important aspect is to continue supporting and engaging in research about the use of specialized immunoglobulin products against certain diseases like cytomegalovirus (CMV) in transplant recipients.

RICHARD: We recognize what is potentially a very scary situation. The Alzheimer’s situation could overwhelm the demand for product beyond what any single company, or all the companies combined could actually supply. I hope the Alzheimer’s studies are done with complete rigor, because if there’s even a hint of improvement in Alzheimer’s through the use of plasma products, the demand will be strong. If sketchy data is being promoted as quite promising and it’s not actually very impressive, it may be presented as the next best thing to happen in Alzheimer’s, which affects millions of people.

MARCIA: You need guidelines for managing patients, but when they’re too specific, insurance companies can really misuse them. If there’s a dosage recommendation in guidelines, the insurance companies will choose the lowest dosage even for patients who need a higher one. The insurance companies often deny the claim, especially in some areas of common variable immune deficiency. The more physicians try to put as many specifics as possible into guidelines, they can be misused and we’re seeing that happen often. The more we have the data to back up dosage treatment, the better it will be. In primary immunodeficiency, the data is not always there.

RICHARD: Guidelines can be extremely helpful, but the problem is when they are used as rigid policy.

JOHAN: In Europe, discussions about dosage restrictions are linked to the development of health technology assessment (HTA) where they’re looking at dosage, efficacy and costs. We have to be very careful in the area of HTAs. We need to provide good data. It’s definitely an emerging issue, even outside the context of guidelines.

DENNIS: What’s the role of the patient groups, industry and physicians to educate people so they’re making the right decisions?

PATRICIA: Part of patient advocacy is to get to the insurance companies and educate them about treatment and the needs of patients. Insurance companies cannot take a cookie cutter approach to the treatment of patients. Not everybody is going to react in the same way. Educating Medicare and insurance providers is a priority for us.

DAVID: You need the data to back that up. That’s the vital thing.

FRED: We’re doing a multi-center research study that will give us data to take to third-party payers and other organizations.

RICHARD: We’re finding the same in the neuropathy world. There’s some interest in studying immunoglobulin levels after treatment. Right now in the neuropathy world, peak levels may be as just as important as trough levels. We’re looking at that and
what it tells us about treatment options. The American Academy of Neurology has a
guideline group. The guidelines have to be reviewed every few years and the evidence
has to be re-analyzed. Some of these guidelines are based on limited data. It becomes
a consensus. For some people, we must individualize the guidelines. But others who
are looking to cut costs use guidelines for their purpose. It’s always a problem.

BERNADINE: At CSL Behring, we continue to do studies including registration
studies and investigator-initiated studies, and to emphasize the outcomes.

RICHARD: A lot of studies are short-term. One of the problems is that we don’t
always have the long-term data, which is really the microeconomic impact, because it’s
hard to fund studies for many years. But if there’s a way to capture some of the data
on some of these studies and follow these patients for a number of years, it would be
helpful in terms of developing this information.

PATRICIA: We are putting together a CIDP Patient Outcome Study with that in
mind, following the patients every two years. The survey will also have questions about
reimbursement and advocacy.

JOHAN: In Europe, we’ve been promoting a subclass of rare diseases called rare
plasma-related disorders. They bring together hemophilia, PID, GBS and CIDP among
others. It’s very beneficial. There was a roundtable of stakeholders in France, and
people from prominent rare disease institutions are looking at the issue of rare
plasma-related disorders. If you have orphan drug status you will get exemptions and
automatic reimbursement. We are exploring having specific stages for plasma protein
therapies, which face similar challenges.

MARcia: When we get together at the IPOP meetings and at the Plasma Protein
Therapeutics Association (PPTA), that’s a way of bringing many of us together. A Plus
sent a strong letter of support for the Dublin consensus conference. For instance, we
are concerned about any relaxing of the standards on blood collection safety. That’s an
issue for the whole world because so much plasma comes from the US. It’s not just a
US concern; it has global impact.

CHRIS: I think there is a special role for patient organizations. We’re there trying to
solve some of those problems as a larger community.

RICHARD: We talked earlier about the microeconomic benefit of treatments. But
we’re talking to two different types of groups. The government may care about the
microeconomics, but the insurance companies and the physicians care about their
reimbursement. We don’t have an adequate way of dealing with both those issues.

DENNIS: The United States passed comparative effectiveness research that
became part of the healthcare reform legislation and we have health technology
assessment in Europe. What are your views on these approaches?
**RICHARD:** I have major concerns with comparative effectiveness. I think we would all agree that if we can identify ineffective therapies, we don't want to use them. Comparative effectiveness means that some are better than others, but we already know that in our individual patients. The driving force is economics, not patient care. Our patients are potentially at risk for being comparatively taken out of the system, because the treatment that works for them is not economically good enough compared to others that work better for some patients. It's going to be important for the doctors and the patient advocates to make sure this is used in a way that doesn't hurt patients.

**MARCIA:** With A Plus our whole issue was that when they started comparative effectiveness, they left out clinical. It was all cost. We were successful in saying it has to be based on clinical effectiveness, not cost.

**JOHN:** We come back to the issue of lack of evidence. Let's take plasma products as an example where things tend to be generic in comparing different products or different routes of administration and different bioavailabilities among different diseases. All of these things impact the effectiveness and cost. A patient who has CVID and a protein-losing enteropathy is going to cost more than a patient who has X-linked agammaglobulinemia and is easier to manage. They're apples and oranges, but we tend with cost to lump everybody together. What really needs to be done is to talk about the cost of a specific diagnosis and its complication, and how that impacts the microeconomics. And so you have to go after this with a scalpel and not with a sledgehammer.

**DENNIS:** Given rare disease populations are small, what are the issues with applying comparative effectiveness research to rare diseases and having what is deemed sufficient evidence?

**MARCIA:** A Plus nominated an individual from the hemophilia community to sit on a rare disease panel. We have someone from the plasma community on this panel. This is an area that we just have to watch very closely.

**JOHAN:** In Europe, the HTA agencies are organizing themselves very efficiently. It's very important that the patients talk to each other. We are very pleased that a PID stakeholder has an official seat on the rare diseases steering committee of the European commission. In France, the HTA agency is looking at a post-marketing study comparing subcutaneous to IV. Industry and the doctors are not happy about that, but the HAS, which is the HTA agency in France, is trying to push this issue forward. I know there's a stakeholder joint effort to try to stop that, but that is one example of how it could be coming for immunoglobulin as well.

**MARTINE:** France would like to be self-sufficient with plasma products, which is not a good issue for patients. At the moment, we have no problem with reimbursement in France, but we will have the problem of choice.
**DAVID:** There is an organization mantra about unpaid donors being the better donors. It is very insulting for Europe to even think about that because we rely on the rest of the world for 70% of our plasma products in Europe. Yet, the European Commission waved the banner saying unpaid donors are the way to go. It’s the big lie. It’s an issue all the way from the World Health Organization downward because the World Health Organization recently published a paper on plasma products where they re-emphasize this groundless policy that has no basis in fact or science. This could hurt patients by reducing the availability of therapies.

**DENNIS:** The Dublin consensus conference basically is trying to make people aware that taking this to an extreme could really compromise patient care?

**DAVID:** In January 2011, we’ll be having a follow-up meeting in Dublin. We will look at the two areas that divided us: one is the paid versus the unpaid donor and the other is blood donor versus the plasma donor.

**RICHARD:** In the US, we need to get our government institutions that fund research to recognize the importance of our diseases.

With the Internet, patients are becoming more knowledgeable about their own disorders than their primary care doctor who sees one case in 10,000. Maybe we need to do more to make sure patients are aware of their own red flags and ask their primary care doctor. Empowering the patient is a very powerful tool in promoting awareness of our diseases.

**MARCIA:** We completed an Internet survey. The results are interesting. Patients who are either seen at major medical centers or are connected to a patient organization, are getting better care than those seen at physician offices or non-university hospitals. We should do everything we can as patient organizations to be on the Internet and helping people get the resources they need for better care.

**PATRICIA:** That’s happening with the GBS and CIDP populations as well. We get requests daily from around the world from people who are experiencing symptoms but don’t know where to go for accurate diagnosis. We immediately send out educational information. We also have a physician referral list which we use to connect patients with physicians who have experience in diagnosing and treating inflammatory neuropathies. Patient education is empowering.

**Political issues**

**JOHAN:** In Europe, rare diseases are being looked at very seriously by health authorities. We are seeing the implementation of national rare disease plans. A unanimous recommendation is the need to empower and inform patients. There’s value in bringing together people from different rare diseases backgrounds. We’ve seen progress through working with patient groups at the European level in the
plasma protein and PID areas. We have a platform called Plus. It highlights that most issues are common issues to all rare disease patient groups. We find even more specific common issues among patients using plasma protein therapies.

**MARcia**: In the United States, we have A Plus. We brought together plasma users—JMF and IDF, GBS and also hemophilia and Alpha 1. The plasma users worked together on some health care reform issues such as lifetime caps that affect individuals with rare, chronic diseases. We have so many common issues with other plasma users and we’re so much stronger together.

**MARTINE**: In France, the financial situation is complicated. As a patient group, we have to address the health authorities to keep the patients with rare diseases on their priority list.

**MARcia**: Since 1995, we’ve surveyed and quantified our patient population’s health status before and after diagnosis. When you’re advocating on Capitol Hill, that data has an impact. There are very few disorders in which an intervention is as dramatic as it is with immunoglobulin for primary immune deficiency. We want to show insurance companies the long-term benefits of early diagnosis and being on immunoglobulin. Some insurance companies are only looking to the next two to three years regarding how long they’re going to cover a patient, rather than long-term savings.

**DENNIS**: Can we combine all this data into a strong portfolio of evidence to convince policymakers?

**JOHAN**: We’re talking about the macroeconomic cost benefit approach of early identification of the patients. After looking at the impact of missed work and hospitalizations, consider what the payer organizations within the governments want to see. Often they’re only looking at the price, not the cost benefit of a treatment. In Europe, we do not yet have this sort of data, but IPOPI is actually looking into it. Hopefully, in the future we’ll be able to have similar data. In the meantime, we can use data produced for the US because I think it will hold true for all regions.

**VICKI**: That’s where constant advocacy comes in.

**DAVID**: We have just been involved in advocacy training along with the hemophilia community in Europe. That has had a dramatic effect in those countries. Suddenly, the patient organizations have realized the tremendous benefit in doing surveys and having statistics and data.

**Registries**

**CHRIS**: Clinical registries are important for capturing information about patient volume, diagnosis and treatment, something that’s been sorely missing and is still missing in a number of countries. It’s very difficult to advocate with only partial
information. In the UK we have funded the establishment of a comprehensive PID patient registry. This includes the IT systems needed to capture data, and the services of a documenter to assist PID centers with initial data entry and with updating data at regular intervals.

**MARCIA:** Across the Atlantic, the USIDNET patient registry uses many of the same questions as the European Society for Immunodeficiencies (ESID), so there can be a lot of commonality. It’s not the same registry for many reasons, but a lot of the questions were designed to enable international collaboration.

**RICHARD:** There are some national registries for the neurological and the GBS side. The Netherlands has a strong registry for the immune neuropathies. In the last five years, the Inflammatory Neuropathy Consortium developed through the Peripheral Nerve Society. This consortium is an international group of centers looking at immune neuropathies. We have a Web-based registry for international patients with immune neuropathies. We’re starting with multi-focal motor neuropathy, and we’re hoping to expand that to a registry of all the inflammatory immune neuropathies. We’re a bit behind the PID world with registries, but we have more difficulty identifying treatment outcomes. It’s based on disability and we don’t have a lot of data.

**MEL:** We support registries and studies. All of our licensing studies have recorded outcomes. We’ve accumulated a lot of licensing studies and we have a large database that we’re mining for meta-analyses such as the changes in doses and outcomes over years. This will result in publications.

**HANS-PETER:** European medicine agencies and European regulatory agencies have mandated companies to provide health economic data in addition to clinical outcome data. It’s important to convince the authorities that interventions are economically reasonable.

**Innovation**

**DENNIS:** I would like to hear about innovations that will be occurring with immunoglobulins including therapies, how they are delivered and education. How does the future look?

**FRED:** The patient organizations and the physicians look to industry to develop innovative products and delivery systems to make life better for the patients and for the doctors. The spotlight shines on the companies to develop the breakthroughs that really impact the lives of the patients.

**MEL:** We see already the development of the 20% subcutaneous product, which should extend the ability to use subcutaneous into the neurological and inflammatory diseases and will make treatment easier for the immune deficiencies. We continue to improve the yield to assure supply and always keep ahead of the safety issue.
JOHN: An aspect of innovation that is a real opportunity for both neurological and immune deficiency is the use of adjuvant therapies for the complications of immune deficiency. In our practice, even patients who are getting optimal doses of immune globulin replacement therapy have multiple complications associated with their underlying condition, whether that's an increase of malignancy or immune disease. There's very little research being done in that area and very little in the way of innovation in terms of management of secondary conditions associated with primary immune deficiencies.

HANS-PETER: It will be worthwhile to reconsider combination approaches using IVIg in the neurological world. Another interesting area is modulating the part of the IgG molecule which binds to the body's effector cells.

MEL: We will likely see development of enriched IgG products, both for special activities such as anti-inflammatory versus anti-microbial activities and products that have fewer adverse effects. Some possible examples are a product with a lower potential for hemolytic activity, products that have increased activity in the inflammatory and autoimmune diseases, and more specific hyperimmunes. There are opportunities to segregate plasma from people who have certain high titers and other ways of selecting plasma and/or modifying the final product to remove or enrich certain specificities as well as the modifications of the effector functions.

DAVID: The ultimate innovation that people with primary immunodeficiency or reliance on immunoglobulin look forward to is the one that eliminates the need for immunoglobulin. A close second is the ability to take it in tablet form or something that doesn't involve the inconvenience of needles and sterile kits and all that. How near are we to that?

MEL: Other than the possibility of topical treatments for the GI or respiratory tract, I don't really see that we're going to have a way of administering an immunoglobulin-size molecule into the bloodstream without injection. But I do think we've seen the benefits of subcutaneous in comparison to intravenous.

HANS-PETER: Is there any research on whether one IVIg product can be considered superior to the other based on specific constituents that may target one autoimmune disease?

MEL: We have the examples of anti-D to prevent sensitization of the mother. We have CMV hyperimmune globulin for patients at risk for CMV. I think we'll see some continued differentiation in this way, but it depends on identifying the antigens, which lags behind the use of polyclonal IVIg. There's potential, but I think we need a lot of work on identifying the antigens first. Another example is the use of IVIg where there's really no substitute, as in Kawasaki disease. We still don't know the cause or the antigen. We're still a long way from a differentiated product.
DENNIS: What would be your highest priority for treatment of people with immune deficiency? Is there an opportunity to share something across the Atlantic?

FRED: My priorities are earliest possible diagnosis, equal access to affordable treatment, resistance to the notion of self-sufficiency and donated versus un-donated plasma collection, the development of new therapies, new research and delivery systems by industry. You really have five pieces: the patients, the physicians, industry, the media and government.


DAVID: Safety.

MARCIA: Empowerment of patients and how to deal with the healthcare system, their physicians and with governments.

DAVID: If we can motivate our patient groups, we’ll see a change.

CHRIS: There should be some kind of major platform for all this information so that it is available across national and international boundaries. There’s a lot of information to share. I know IPOPI and others are trying to establish this and I applaud their efforts.

RICHARD: In neuropathy, while IVIg has clearly been a very effective treatment, we really need to understand our diseases better in order to move forward. We really need to work on the physiology of our disorders, which requires patient advocacy to get grants because optimal treatment depends on understanding the disease. We need to campaign at the National Institutes of Health and the European equivalent and make it a priority to better understand our diseases.

DENNIS: There are data and programs in different places that clearly need to be shared. I know patient groups and physicians are trying to do that. Hopefully, with this dialogue, we’ve done some of that and this will be shared globally. It is important to continue the conversation, share information and continue our efforts to optimize patient care. Thank you so much for your participation and for coming all this way.

The views and opinions expressed in this Key Issues Dialogue are those of the participants and do not necessarily reflect the official policy or position of CSL Behring.
About the Participants

Marcia Boyle

President and co-founder, Immune Deficiency Foundation (IDF)

Marcia Boyle has developed many of the patient and medical programs for which IDF is known. She also serves on the board of the International Patient Organization for Primary Immune Deficiency Diseases (IPOPI), of which she is a co-founder. She has been a patient advocate for nearly 30 years since starting IDF in reaction to the diagnosis of her son, John, with x-linked agammaglobulinemia. She has served as director of departmental programs and capital projects and director of principal gifts for the fund, Johns Hopkins Medicine, and director of development for Wilmer Eye Institute and Neurology and Brain Sciences, Johns Hopkins Medicine.

Patricia A. Bryant

Executive Director of the GBS/CIDP Foundation International

After her recovery from Guillain-Barré syndrome in 2003, Patricia Bryant volunteered as liaison to GBS/CIDP for Nassau County, NY, regional director for New York and New Jersey, and she served on the Board of Directors of the Foundation from 2006 until her recent appointment as executive director. A hospice volunteer since 1992, she was honored by the State of New York and Nassau County for her work in providing patient care and support to the terminally ill and their caregivers.

Dr. Hans-Peter Hartung

Professor and Chairman, Department of Neurology, Heinrich-Heine-Universität Düsseldorf

Hans-Peter Hartung's clinical and research interests are in the field of basic and clinical neuroimmunology, and in particular multiple sclerosis (MS). He was professor and head of the MS clinical research group at the University of Würzburg, and he has been a steering committee member in numerous international multi-center therapeutic trials in MS, Guillain-Barré Syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP). He has authored or co-authored more than 540 articles in peer-reviewed journals and edited nine books.

Christopher Hughan

Chief Executive, Primary Immunodeficiency Association, UK

Chris Hughan has been CEO of the UK Primary Immunodeficiency Patients Association (PiA) for six years and has worked in the non-profit sector in the UK and USA for over 15 years. Prior to this he was a senior executive in the advertising and public relations business, working for major international agencies such as Ogilvy & Mather, McCann Erickson and J Walter Thompson in the UK, USA and Australasia. Chris is passionate about helping children and adults with inborn immune disorders as he has had a chronic auto immune disease since childhood.
Dr. Gerd Klock  
**Biochemist, Senior Scientist-R&D, representative of DSAI on primary immune deficiencies**

Gerd Klock has worked on medical research topics such as cancer, cardiovascular diseases and wound healing. His present research interests are focused on diseases with aspects of immunology and inflammation. In a number of biotechnology companies in Germany Dr. Klock was a senior scientist in research and development. He has served as local representative of the patient organization DSAI on primary immune deficiencies since 2005.

Dr. Richard A. Lewis  
**Professor and Associate Chairman of Neurology, Wayne State University School of Medicine**

Richard Lewis has been specializing in disorders of the peripheral nervous system since he completed his residency in neurology at the University of Pennsylvania in 1978. He has been particularly interested in demyelinating neuropathies, including inherited disorders and inflammatory and immune mediated conditions. He is on the Medical Advisory Board of the GBS/CIDP Foundation International, the Board of Directors of the Peripheral Nerve society and the Steering Committee of the Inflammatory Neuropathy Consortium. He identified the multifocal demyelinating neuropathy now called the “Lewis-Sumner Syndrome.”

Vicki and Fred Modell  
**Co-Founders, Jeffrey Modell Foundation**

Vicki and Fred Modell founded the Jeffrey Modell Foundation in 1987 in memory of their son Jeffrey who died at the age of 15 from complications of primary immunodeficiency. JMF is a global nonprofit organization devoted to early and precise diagnosis, meaningful treatments, and ultimately cures through clinical and basic research, physician education, patient support, advocacy and public awareness. The Modells have established 75 Jeffrey Modell Diagnostic and Research Centers in the US, Canada, Africa, Asia, Australia, Europe, Latin America, and the Middle East.

Martine Pergent  
**Co-founder of IRIS, the organization for primary immunodeficiencies in France**

Martine Pergent has been a consultant to IRIS since its creation in 1999. She works together with the association in strategic planning, patient surveys about immunoglobulins, publications, awareness campaigns and relations with pharmaceutical companies, public health authorities and other stakeholders in the field of plasma collection or rare diseases. In 2004, she was elected to the Board of IPOPI. Committed to advocating on behalf of patients with PID at the national, European and global levels, she created and is responsible for the immunoglobulin global list available on www.IPOPI.org.

Dr. John W. Sleasman  
**Robert A. Good Professor and Chief-Division of Allergy, Immunology, and Rheumatology, University of South Florida, Department of Pediatrics**

John Sleasman is certified in pediatrics, pediatric rheumatology and clinical and diagnostic immunology. He is past president of the Southern Society for Pediatric Research and was elected as a member of the American Pediatric Society. He received the Clinical Scientist Research Award from the University of Florida and the Silver Award for Outstanding Research in Pediatric AIDS from Children’s Hospital of Philadelphia. A past chair of the AIDS immunology and pathogenesis studies for the Center for Scientific Review—National Institutes of Health.

Dr. Johan Prevot  
**Director of Global Development, IPOPI**

Johan Prevot has worked in the healthcare sector for 10 years in the field of health policy and public affairs. He is responsible for the growth of IPOPI’s global activities through health policy advocacy campaigns, and for strengthening IPOPI’s national member organizations network. He was previously director of health policy Europe for the Plasma Protein Therapeutics Association (PPTA). Throughout his career he has been an advocate for improving patient access to therapies in the field of rare plasma-related disorders such as primary immunodeficiencies, hemophilia and alpha-1 antitrypsin deficiency.
About the Participants

Health—his research focuses on primary and secondary immune deficiency disorders. His recent publications are related to the use of novel Ig preparations.

David Watters
Executive Director, IPOPI

David Watters has been executive director of IPOPI since January 2005. From 1981 to 1993 he was CEO of the UK Hemophilia Society. This period covered the time when people with hemophilia were shown to have been infected with HIV and HCV. His lobbying led to the award of compensation for HIV infection. From 1994 until 2005, he was CEO of UK RIA. He has been closely identified with work at an international level through IPOPI and the European Patients Primary Immunodeficiency Collaboration.

Dr. Mel Berger
Senior Medical Director in Clinical Research & Development, CSL Behring

Mel Berger’s research has focused on antigen-antibody and complement interactions, primary immune deficiency and control of inflammatory responses. He has been a leader in research on the use of immunoglobulins in human disease and played a key role in developing the use of portable pumps to give IgG subcutaneously. He served as assistant chief of allergy-immunology at Walter Reed Army Medical Center and holds faculty appointments at Case Western Reserve University in pediatrics, pathology and general medical sciences (oncology). He also served as a member and chair of the Allergenic Products Advisory Committee of the Food & Drug Administration.

Bernadine Dixon
Senior Director, Immunoglobulins, Global Commercial Development, CSL Behring

Bernadine Dixon has more than nine years of experience at CSL Behring and its predecessor companies. Previously she was a management consultant at PricewaterhouseCoopers.

Dennis Jackman
Senior Vice President of Public Affairs, CSL Behring

Dennis Jackman has global responsibility for public policy, stakeholder relations and corporate communications. He has held senior Public Affairs positions in the pharmaceutical and biotechnology industry since 1989. Before this, he was a senior aide to US Senator Arlen Specter in appropriations, tax, trade and other business-related areas.

Dr. Michael Bernd Rode
Senior Director, Marketing, Central Europe, CSL Behring

Michael Bernd Rode is the senior director of marketing for Central Europe. After a year in medical marketing with Knoll Pharma he joined Behringwerke GmbH in 1994 as a clinical project manager. He subsequently held marketing positions with Centeon and Aventis Pharma.

Leaders in the PID and neurological disease communities in Europe joined their peers in New York from London to exchange ideas about treatment and other issues involving these disease states.
New York participants (L to R): Dr. Richard Lewis, Dr. John Sleasman, Vicki Modell, Dr. Mel Berger, Dennis Jackman, Marcia Boyle, Patricia Bryant, Bernadine Dixon, and Fred Modell

About CSL Behring

CSL Behring is a global leader in the plasma protein therapeutics industry. Committed to improving the quality of life for people with rare and serious diseases, the company manufactures a range of plasma-derived and recombinant therapies for the treatment of coagulation disorders, primary immune deficiencies, hereditary angioedema and inherited respiratory disease. The company’s products are also used in cardiac surgery, organ transplantation, burn treatment and to prevent hemolytic diseases in the newborn. CSL Behring is a subsidiary of CSL Limited. For more information, visit www.cslbehring.com.
